Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/EP05/003144

International filing date: 24 March 2005 (24.03.2005)

Document type: Certified copy of priority document

Document details: Country/Office: EP
Number: 04007045.0
Filing date: 24 March 2004 (24.03.2004)

Date of receipt at the International Bureau: 18 May 2005 (18.05.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

Europäisches Patentamt	European Patent Office	Office européen des brevets

Bescheinigung | Certificate | Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

04007045.0

EP/05/3144

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

Anmeldung Nr:
Application no.: 04007045.0
Demande no:

Anmeldetag:
Date of filing: 24.03.04
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

CHIESI FARMACEUTICI S.p.A.
Via Palermo, 26/A
I-43100 Parma
ITALIE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

8-hydroxy-5-[(1R)-1-hydroxy-2-[[(1R)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]-2(1H)-quinolinone monohydrochloride in crystalline form and the process for its preparation

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s) revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/
Classification internationale des brevets:

C07D215/00

Am Anmeldetag benannte Vertragstaaten/Contracting states designated at date of filing/Etats contractants désignées lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PL PT RO SE SI SK TR LI

BIANCHETTI • BRACCO • MINOJA
STUDIO CONSULENZA BREVETTUALE

PLEASE ACKNOWLEDGE BY FAX SAFE RECEIPT OF THIS APPLICATION

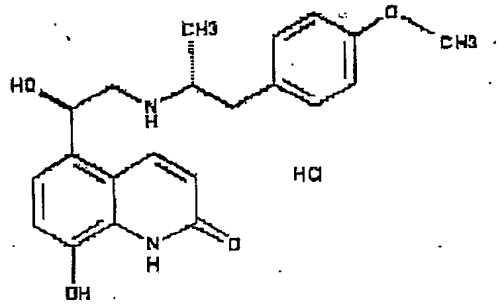
The fee for acknowledgement of receipt is paid in the enclosed Form 1010.

Thank You!

OUR REF: SCB 1370 EUR

8-HYDROXY-5-[(1R)-1-HYDROXY-2-[[(1R)-2-(4-METHOXYPHENYL)-1-METHYLETHYL]AMINO]ETHYL]-2(1H)-QUINOLINONE MONOHYDROCHLORIDE IN CRYSTALLINE FORM AND THE PROCESS FOR ITS PREPARATION

The present invention relates to 8-hydroxy-5-[(1R)-1-hydroxy-2-[[(1R)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]-2(1H)-quinolinone monohydrochloride of formula (I):



(I)

in crystalline form. The invention also relates to the process for the isolation by crystallisation of the compound (I) and to its use for the preparation of pharmaceutical compositions for inhalation in combination with suitable carriers or vehicles.

Background of the invention

8-hydroxy-5-[(1R)-1-hydroxy-2-[[(1R)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]2(1H)-quinolinone monohydrochloride is known from the European patent n. EP 0 147 719 as a bronchodilator provided with a potent beta-2-adrenoceptor stimulating action.

The compound, that has been also defined as 8-hydroxy-5-{(1R)-1-hydroxy-2-[N-((1R)-2-(p-methoxyphenyl)-1-methylethyl)amino]ethyl} carbostyril hydrochloride and identified as TA 2005, has been further

developed by the applicant under the experimental code CHF 4226.

Prior art

The process for the preparation of TA 2005 is described in EP 0 147 719, example 4. In particular, the process for the isolation of the crude product is reported in step (3-a), wherein the insoluble materials obtained after the catalytic hydrogenation of 3.5 g of 8-benzyloxy-5-{(1R)-1-hydroxy-2-[N-((1R)-2-(p-methoxyphenyl)-1-methylethyl)amino]ethyl}carbostyril hydrochloride in tetrahydrofuran (100 ml) and water (10 ml) are collected by filtration and washed with an aqueous 10% ethanol solution. The filtrate and washings are combined, and the combined solution is concentrated under reduced pressure to remove solvent. The residue is crystallised with a mixture of ethanol, water and isopropyl ether, and crystalline precipitates are collected by filtration. 2.38 g of 8-hydroxy-5-{(1R)-1-hydroxy-2-[N-((1R)-2-(p-methoxyphenyl)-1-methylethyl)amino]ethyl}carbostyril hydrochloride are obtained as colorless crystals.

The yield was of 83% and the final product showed the following characteristics:

melting point: 170.0-171.5°C (decomp.)

$[\alpha]_D^{22}$ -64.40° (c = 1.00, methanol)

IR ν_{max}^{nujol} (cm^{-1}): 3300 (broad), 1640, 1610, 1600

Object of the invention

The invention relates to 8-hydroxy-5-[(1R)-1-hydroxy-2-[[(1R)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]-2(1H)-quinolinone monohydrochloride in crystalline form having suitable characteristicsfor the preparation of pharmaceutical compositions for inhalation in combination with suitable carriers or vehicles.

The compound will be identified hereinafter also with the abbreviation CHF 4226.

The compound of the invention is preferably administered by inhalation.

Formulations for inhalation wherein the active compound is in solid form include dry powder compositions to be delivered by a dry powder inhaler (DPI), aerosol compositions comprising a suspension of fine drug particles in a propellant gas to be delivered by a pressurized metered-dose inhaler (pMDI) and aerosol composition in form of aqueous suspensions to be delivered by a nebulizer.

The efficacy of this route of administration can be limited by the problem encountered in making appropriate and consistent dosages available to the lungs.

One of the most important features is to ensure uniform distribution of the active compound in the formulation, particularly when it is highly potent and has to be given in low doses.

Moreover, the solid compound in the composition should be as pure as possible and endowed with the required chemical and physical stability.

In the compositions for inhalation, the active compound should be in form of finely divided particles of a controlled particle size which does not exceed approximately 5 μm, in order to achieve maximum penetration into the lungs.

Said particles are conventionally made by techniques such as micronization or grinding.

Therefore, the active compound should be stable during the micronization process and the particles provided with an adequate degree of crystallinity in order to be sufficiently stable for pharmaceutical use.

The aim of the present invention is thus to provide a stable crystalline 8-hydroxy-5-[(1R)-1-hydroxy-2-[[(1R)-2-(4-methoxyphenyl)-1-methylethyl] amino]ethyl]-2(1H)-quinolinone monohydrochloride.

Another aim of the invention is to provide a process for the preparation of the compound with an adequate degree of crystallinity.

As known in the prior art, after collecting the crude product and washing with an aqueous 10% ethanol solution, the filtrate and washings were combined and the combined solution was concentrated under reduced pressure to remove the solvent.

It has now been found that in the process of isolation of the crude product, when the solution is concentrated under reduced pressure to remove the solvent, the volume to which the solution is reducedis critical. It has indeed been found that the solution should be concentrated to a volume equal to or higher than 1/3 of its initial volume. Moreover the isopropyl ether has to be added to the concentrated solution slowly, in not less than 5 minutes and at a temperature higher than 30°C.

The above conditions allow to obtain an homogeneous final solvent mixture and the regular crystalline growth.

In fact it has been found that if the volume of the concentrate of the crude product is too low and in particular lower than 1/3 of its initial volume and the addition of isopropyl ether is effected too fast, for example in less than 5 minutes, the highly concentrated crude compound rapidly precipitates, thick unfilterable slurries are formed, the product incorporates high levels of mother liquors consisting of solvents and impurities andit is difficult to isolate. Moreover, when isolated and dried, it includes a significant amount of impurities.

Furthermore, the product contains a high amount of amorphous material and, as highlighted before, particles of amorphous structure can cause a number of problems when included in inhalation formulations: in fact this kind of particles are extremely cohesive, tend to stick together and tend to absorb ambient moisture at their surfaces with time.

So there is the need for a product in a substantially pure crystalline form.

The present invention provides CHF 4226 in a crystalline form and a process forpreparation thereof.

In order to prepare the crystalline product of the invention, crude 8-hydroxy-5-[(1R)-1-hydroxy-2-[[(1R)-2-(4-methoxyphenyl)-1-methylethyl] amino]ethyl]-2(1H)-quinolinone monohydrochloride which has been obtained for example according to the method disclosed in EP 0 147 719 is dissolved in a suitable solvent.

A suitable solvent is a protic solvent such as ethanol, isopropanol and their aqueous mixtures. The preferred is an ethanol-water mixture.

The most suitable recrystallisation solvent mixture is an ethanol-water mixture in a ratio from 97:3 to 95:5 v/v. Advantageously, an intermediate step of distillation of the ethanolic solution under reduced pressure is carried out, to remove residual isopropyl ether from the mixture as well as to improve the yield.

The recrystallisation process according to the invention allows an effective removal of the impurities up to levels equal to or lower than 0.5%, preferably 0.2%, even more preferably 0.1% in order to obtain the product in a pure crystalline form provided with suitable characteristics to be used for the preparation of pharmaceutical compositions for inhalation in combination with suitable carriers or vehicles.

Detailed description of the invention

The method of EP 0 147 719 involves the filtration of an aqueous ethanol suspension obtained after the catalytic hydrogenation of 8-benzyloxy-5-{(1R)-1-hydroxy-2-[N-((1R)-2-(p-methoxyphenyl)-1-methylethyl)amino] ethyl}carbostyril hydrochloride to remove the catalyst and the washing with ethanol. According to the present invention the solution obtained after the

filtration is concentrated under reduced pressure, preferably comprised between 200 and 400 mbar at a temperature between 30°C and 55°C, preferably at 45-50°C to a volume comprised between ½ and 1/3 of the initial volume. Then diisopropyl ether is slowly added to the warm solution under stirring. The addition of diisopropyl ether is performed in at least 5 minutes, preferably in 20-30 minutes.

The mixture is then cooled under stirring at a temperature between 0°C and 10°C for 1 to 2 hours and the solid is isolated and washed with ethanol.

The wet crude product is suspended in ethanol, heated under reflux at 75-78°C and slowly added with water until a clear solution is obtained. The solution is filtered and the filter is washed with ethanol. The warm solution is concentrated, under stirring, under reduced pressure, at 40-50°C, up to about from ½ to 1/3 of its original volume. The product begins to crystallise from the solution giving rise to a suspension. The suspension isslowly cooled and kept at a temperature from about 0 and 10°C, preferably from about 0 to 5°C, for at least 1 hour and up to 20 hours or more, under stirring. The solid is recovered by filtration, washed with ethanol and finally dried in a conventional manner, for example by air drying, drying under reduced pressure, or drying in the presence of a sterile inert gas to give the crystalline compound.

The 8-hydroxy-5-[(1R)-1-hydroxy-2-[[(1R)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]-2(1H)-quinolinone monohydrochloride obtainable using the method described above was investigated to determine: the melting point by DSC, the specific optical rotatory power $[\alpha]_D^{20}$, the enantiomeric purity by capillary zone electrophoresis, the amount of total impurity by HPLC and the X-ray powder diffraction (XRD) pattern.

The 8-hydroxy-5-[(1R)-1-hydroxy-2-[[(1R)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]-2(1H)-quinolinone monohydrochloride of the

present invention is therefore characterized by:

a melting range of 185-195°C (decomposition), determined by Differential Scanning Calorimetry (DSC) at a scan rate of 10°C/min.;

a specific optical rotatory power $[\alpha]_D^{20}$ (c = 1.00, methanol) of -68.0°;

an enantiomeric purity higher than 99.0%, preferably higher than 99.5%, determined by capillary zone electrophoresis;

impurity levels of less than 0.5%, preferably less than 0.2%, even more preferably less than 0.1%, determined by HPLC;

a X-ray powder diffraction pattern identical or substantially identical to that listed under the example below. Suitably the compound has *inter alia* one or more of the following characteristic XRD peaks: 12.25; 3.63; 16.37; 18.03; 18.35; 19.29; 19.96; 21.44; 21.93; 22.85; 23.61; 24.25; 24.99; 26.68; 27.66; 28.61; 29.48; 29.94; 30.61; 31.86; 32.22 and 33.95 ± 0.1 degrees /2 theta.

The following example illustrates the present invention.

EXAMPLE

Crystallisation of 8-hydroxy-5-[(1R)-1-hydroxy-2-[[(1R)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]-2(1H)-quinolinone monohydrochloride

(CHF 4226 monohydrochloride)

The suspension obtained after the catalytic hydrogenation of 8-benzyloxy-5-{(1R)-1-hydroxy-2-[N-((1R)-2-(p-methoxyphenyl)-1-methylethyl)amino] ethyl}carbostyril hydrochloride (100 g in 1000 ml of ethanol and 100 ml of water) was filtered on a celite pad and washed with ethanol (300 ml). The filtered solution was concentrated in a rotary evaporator (Tbath = 55°C; vacuum = - 0.8 bar) until residual volume was about 600 ml. Isopropyl ether (560 ml) was dropped in the warm solution (T = 45-50°C) during 30 min. The suspension was cooled at 5-10°C and stirred for 60 minutes, then it was filtered in a Buckner filter washing the solid with ethanol (200 ml).

The wet crude 8-hydroxy-5-[(1R)-1-hydroxy-2-[[(1R)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]-2(1H)-quinolinone monohydrochloride (154.6 g; corresponding to 73 g if dried at 60°C under vacuum) was suspended in ethanol (580 ml) and the mixture was heated at 78°C under reflux; water (25 ml) was slowly dropped in until the mixture was clear. The hot solution was filtered in a Buckner filter, washing with ethanol (150 ml). The filtered solution was concentrated under vacuum (Tbath = 55-65°C; vacuum = 250-300 mbar; Tsolution = 45-48°C), distilling about 360 ml of solvent. Vacuum was disconnected and ethanol (390 ml) was added to the residual suspension, stirring at 45°C until the layer of product on the reactor walls was suspended. The suspension was cooled at temperature lower than 5°C in 90 min., then it was kept at 5°C for 20 hours. The suspension was filtered in a Buckner filter, washing with ethanol (150 ml). The solid was dried under vacuum at 60°C for 24 hours, getting 58.4 g (80.0% yield of the re-crystallisation of 8-hydroxy-5-[(1R)-1-hydroxy-2-[[(1R)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]-2(1H)-quinolinone monohydrochloride.

The product has the following characteristics:

- melting range 190-194°C (decomposition), determined by Differential Scanning Calorimetry (DSC) at a scan rate of 10°C/min.;

- specific optical rotatory power $[\alpha]_D^{20}$ (c = 1.00, methanol) = -68.0°;

- enantiomeric purity higher than 99.5%, determined by capillary zone electrophoresis;

- total impurities: less than 0.15%.

- the X-ray powder diffraction (XRD) pattern is shown in Figure 1 and is represented by the following major peaks:

Angle [°/2 θ]	Rel. Int. [%]
12.25	21.0
13.63	54.2
16.37	64.9
18.03	37.5
18.35	44.5
19.29	50.1
19.96	11.5
21.44	55.8
21.93	100.0
22.85	35.6
23.61	36.9
24.25	88.4
24.99	21.4
26.68	32.5
27.66	21.2
28.61	22.6
29.48	30.5
29.94	14.8
30.61	17.0
31.86	12.8
32.22	11.1
33.95	20.4

CLAIMS

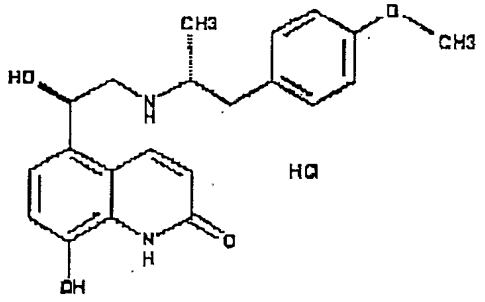
1. 8-hydroxy-5-[(1R)-1-hydroxy-2-[[(1R)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]-2(1H)-quinolinone monohydrochloride characterized by a melting range of 185-195°C determined by Differential Scanning Calorimetry and a X-ray powder diffraction pattern having *inter alia* one or more of the following characteristic peaks: 12.25; 3.63; 16.37; 18.03; 18.35; 19.29; 19.96; 21.44; 21.93; 22.85; 23.61; 24.25; 24.99; 26.68; 27.66; 28.61; 29.48; 29.94; 30.61; 31.86; 32.22 and 33.95 ± 0.1 degrees /2 theta.

2. A process for the preparation of a compound as claimed in claim 1 comprising crystallizing or re-crystallizing the compound from an aqueous ethanol solution added with diisopropyl ether wherein the aqueous ethanol solution is concentrated to a volume comprised between ½ and 1/3 of the initial volume and the addition of the diisopropyl ether is performed in at least 5 minutes.

ABSTRACT

8-HYDROXY-5-[(1R)-1-HYDROXY-2-[[(1R)-2-(4-METHOXYPHENYL)-1-METHYLETHYL]AMINO]ETHYL]-2(1H)-QUINOLINONE MONOHYDROCHLORIDE IN CRYSTALLINE FORM AND THE PROCESS FOR ITS PREPARATION

The invention relates to 8-hydroxy-5-[(1R)-1-hydroxy-2-[[(1R)-2-(4-methoxyphenyl)-1-methyl ethyl]amino]ethyl]-2(1H)-quinolinone monohydrochloride of formula (I) in crystalline form, provided with suitable characteristics in order to be used for the preparation of pharrmaceutical compositions for inhalation in combination with suitable carriers or vehicles and the process for its preparation.



(I)

TELEFAX TRANSMISSION

From: MINOJA, Fabrizio, Dr.
BIANCHETTI BRACCO MINOJA SRL
Via Rossini, 8
20122 MILANO MI (Italy)

Telefax n. (02) 783078
Tel (02) 76021218 - 76021192

To: **EUROPEAN PATENT OFFICE**
Erhardtstraße 27
D-80298 MÜNCHEN
Germany

This transmission consists of ..20..... pages, including this cover page.

If the transmission is not clear, please call or fax.

COMMENTS/MESSAGES

Request for grant of a European Patent:

"8-HYDROXY-5-[(1R)-1-HYDROXY-2-[[(1R)-2-(4-METHOXYPHENYL)-1-METHYLETHYL]AMINO]ETHYL]-2(1H)-QUINOLINONE MONOHYDROCHLORIDE IN CRYSTALLINE FORM AND THE PROCESS FOR ITS PREPARATION"

in the name of: **CHIESI FARMACEUTICI S.p.A.**

Our ref.: SCB 1370 EUR

The confirmation copy follows by DHL

Milano, 24 March 2004